Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

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**Progesterone Receptor Interactions with Cell Cycle Regulatory Molecules Promote Breast Tumor Initiation and Progression.**

**Investigator(s):** Carol Lange, PhD
**Fellow:** Gwen Dressing, PhD
**University of Minnesota at Twin Cities, Minnesota**
**Awarded:** $180,000
**Grant Mechanism:** Post Doctoral Fellowship - Basic Research
**Research Focus:** Biology

Public Abstract:
This year more women will be diagnosed with breast cancer than any other cancer, and while recent years have seen great strides in our ability to manage or cure breast cancer, it is still the second leading cause of cancer-related death in women. Progesterone, a steroid hormone made by the ovaries, acts by binding to a protein receptor, the progesterone receptor (PR), present only in specific target cells. The result of PR activation by progesterone is regulation of genes responsible for cell growth and survival. In breast tissue, these signals contribute to normal breast development during puberty and pregnancy. While PR drives normal breast development, it is present in only a small fraction of non-proliferative (not actively dividing/growing) breast cells in the normal condition. Alternatively, 70% of breast tumors are PR positive upon diagnosis. Thus, at some time during breast tumor development, PR positive cells, which are normally non-proliferative, begin to divide and grow. Recent clinical studies implicate progesterone/PR in breast tumor development, as women taking hormone replacement therapy containing progestin (synthetic progesterone) were more likely to develop breast cancer than women taking similar therapies that did not contain progestin. Uncontrolled cell proliferation is one of the early events that occurs in normal cells leading to cancer. Cell proliferation is governed by the interplay between proteins that promote or inhibit progression through the cell cycle ultimately leading to cell division; the proteins that regulate cell division are often disregulated in newly formed tumors. Interestingly, PR activity is heavily influenced by cell cycle regulatory proteins. The mechanisms of these interactions are not fully understood. Our data suggest that PR interacts with cell cycle proteins, perhaps interacting with them to drive increased cell division, even when progesterone levels are low. We propose that PR activity is coupled to breast cancer cell cycle progression via direct interactions between PR and cell cycle regulatory proteins which then cause PR to activate specific tumor growth genes relevant to breast cancer progression. We will test this idea by synchronizing PR positive and negative breast cancer cells in multiple phases of the cell cycle, and then examining their response to progesterone. We will analyze the genes that are activated by PR/progesterone in a cell cycle dependent manner and assess the necessity for interaction between PR and specific cell cycle regulatory proteins to activate a subset of genes which promote cell growth. We propose to create and analyze a mouse model in which we force breast tissue to express PR while decreasing levels of the cell cycle inhibitory protein, p27; loss of p27 is a common early event in breast tumor formation. We hypothesize that high PR and low p27 levels (recapitulating the initiation of human breast cancers) will result in inappropriate breast cell proliferation ultimately resulting in tumors. Understanding the early events that lead to breast
cancer development such as loss of cell cycle control resulting in inappropriate proliferation of PR positive cells may lead to new treatment options for women at high risk for developing breast cancer. Indeed, recent studies using rat models suggest that treatment with anti-progestins (which block PR activity) prevented breast tumor development. Additionally, understanding how PR interacts with cell cycle regulatory proteins in established breast tumors may lead to the development of new treatment options (such as new, more effective anti-progestin treatments) for advanced breast cancer.

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